



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Donald W. Petersen et al. Art Unit : 1651
Serial No. : 09/327,761 Examiner : J. Witz
Filed : June 7, 1999
Title : BONE GRAFT SUBSTITUTE COMPOSITION

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Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO ACTION MAILED JULY 31, 2001

Claims 2, 3, 8, and 12-28 (attached for the Examiner's convenience) are presented for examination. Claims 2, 8, 12, and 35 are in independent form. All the claims require a bone graft substitute composition having a calcium sulfate, a mixing solution, a cellulose derivative, and demineralized bone matrix or a bioactive agent.

The Examiner rejected claims 2, 3, 8, and 12-38 under 35 U.S.C. §103(a) as being unpatentable over Yim (U.S. Patent No. 5,385,887), O'Leary (U.S. Patent No. 5,484,601), and Jefferies (WO 96/39203) taken as a whole. In a telephone conversation with the undersigned representative, the Examiner clarified that the rejection is based on Yim and O'Leary, and that Jefferies is relied on for suggesting compositions having demineralized bone matrix along with calcium sulfate and a carrier such as a cellulose derivative.

In particular, to reconstruct the compositions covered by the claims, the Examiner relied on O'Leary for disclosing a composition having demineralized bone matrix and a cellulose derivative, and on Yim for disclosing a composition having a calcium sulfate and a cellulose derivative. The Examiner stated:

In the instant case, an analysis of the Applicants' invention shows clearly that all of the components of Applicants' invention are known to be included bone

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graft compositions for their individual and well known contributions to the success of said compositions.

....
...both references include components of the claimed invention and both references explain the contributions of these components to a bone graft composition. There is no suggestion or expectation that the addition of calcium sulfate to the composition of O'Leary would render it ineffective for the intended purpose; to the contrary, the addition of the calcium sulfate is disclosed as being appropriate for use in bone graft compositions. While none of the references individually disclose the combination of the two components of the claimed composition, it would have been obvious to one of ordinary skill in the art to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the exact same purpose. The idea of combining these compositions flows logically from their having been individually taught in the prior art.¹

Applicants remain unclear on how the Examiner is combining Yim and O'Leary to obtain the compositions covered by the claims. In particular, it is not clear whether the Examiner contends that a person of ordinary skill in the art would have been motivated (1) to combine an entire composition from Yim with an entire composition from O'Leary to obtain a composition that includes (among many other components) the components required by the claims, and/or (2) to combine particular components (in particular, calcium sulfate) from Yim's composition with O'Leary's composition. The Examiner is again reminded that the basis for combining references

must be clear and particular.... Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence.²

In any event, there is no suggestion to combine O'Leary's and Yim's compositions in whole or in part. As a result, Applicants request that the rejection be withdrawn.

It would make no sense to combine an entire Yim composition with an entire O'Leary composition. Yim designed a specific composition including autogenous blood as a protein sequestering agent, a porous particulate polymer, an osteogenic protein, and calcium sulfate. Yim's goal was to adequately sequester the protein at a specific site using the autogenous blood. O'Leary describes flowable compositions that include bone powder, a liquid synthetic organic

¹ Pages 3 and 4 of the Office Action (emphasis added).

² *In re Dembiczak*, 50 USPQ 1614, 1617 (Fed. Cir. 1999).

material (e.g., glycerol) that functions as a carrier or suspension agent, and, optionally, a thickener such as polyvinyl alcohol or a cellulosic material. O'Leary does not disclose that his composition can be used to sequester an osteogenic protein at a specific site. As a result, a person of ordinary skill in the art would not have been motivated to combine the O'Leary and Yim compositions because they are designed to achieve different goals. Moreover, a person of ordinary skill in the art would want to avoid combining the two compositions because there is no teaching that a composition including all the components mentioned above would achieve the protein sequestering goal set by Yim. In fact, a person of ordinary skill in the art would reasonably expect the combined composition not to work well for that particular purpose.

Furthermore, a person of ordinary skill in the art would not have been motivated to selectively choose components from Yim's compositions and combine them with O'Leary's composition. Here, Applicants do not dispute that the components of the claimed compositions are known and have been used previously in specific bone graft compositions. This, however, is not the proper standard for evaluating patentability. Most, if not all, inventions are combinations, and mostly of old elements. Nevertheless, a combination may be patentable whether it be composed of elements all new, partly new or all old.³ As the Federal Circuit stated in *Northern Telecom, Inc. v. Datapoint Corp.*,⁴

It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there *must* be some teaching, suggestion, or incentive to make the combination by the inventor.

Accordingly, one needs to look at the references as a whole to determine what they disclose about the claimed components, particularly the components' contributions to a bone graft composition.

One skilled in the art reading O'Leary would not be motivated to combine the calcium sulfate from Yim with O'Leary's composition. O'Leary describes flowable demineralized bone powder compositions capable of having widely varying consistency. As specifically defined by O'Leary, the term "flowable"

³ See, e.g., *Rosemount, Inc. v. Beckman Instruments, Inc.*, 221 USPQ 1 (Fed. Cir. 1984).

⁴ 15 USPQ2d 1321 (Fed. Cir. 1990), *cert. denied*, 498 U.S. 920 (1990) (emphasis added).

applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams and fillers.⁵

To provide a flowable material, O'Leary combines the bone powder with a liquid synthetic organic material, e.g., glycerol, that functions as a carrier or suspension agent.⁶ In cases where the composition can quickly or prematurely separate from the carrier or settle out from the composition such that application of the composition is difficult or inconvenient, O'Leary discloses adding a thickener, such as polyvinyl alcohol or a cellulosic material, to change the thixotropic and suspension-keeping characteristics (e.g., consistency) of the composition.⁷

Yim discloses adding calcium sulfate to a composition to improve retention of the composition at a wound site, to reduce formulation setup time, to improve osteoconduction, to reduce preparation time, to improve moldability and handling characteristics, and to improve consistency.⁸ These reasons for adding calcium sulfate, however, are either inconsistent with the type of compositions that O'Leary intended to form or have already been addressed by O'Leary.

For example, improving retention of the composition at the wound site and reducing formulation setup time suggest that the composition should be relatively viscous (so that it could be retained) in a relatively short time (i.e., reduced setup time). However, as clearly defined by O'Leary, in some embodiments, the compositions are intended to be "runny," which suggests relatively low viscosity and relatively long setup time. In embodiments where O'Leary's compositions are intended to be like a putty (e.g., for improved retention and setup time), O'Leary disclosed adding a thickener such as a cellulosic material. One skilled in the art would not be motivated to further add Yim's calcium sulfate because that would be unnecessarily redundant, and as a result, there is no motivation to form Applicants' claimed composition.

What is more, O'Leary already addressed all the other reasons Yim disclosed for adding calcium sulfate. For example, O'Leary addressed improved osteoconduction by disclosing that

⁵ O'Leary col. 3, l. 30-36.

⁶ *Id.* col. 3, l. 15-20.

⁷ *Id.* col. 3, l. 55 - col. 4, l. 6.

⁸ Yim col. 2, l. 51-65; and col. 7, l. 50-59.

glycerol is a preferred carrier because it "exhibits a particularly pronounced capability for dissolving osteogenic proteins present in the bone powder and enhancing the availability of these proteins at the bone repair site."⁹ Yim, however, does not disclose that calcium sulfate improves osteoconduction when used as a carrier for a material such as demineralized bone. O'Leary addressed reduced preparation time by disclosing that the carrier includes organic materials that are flowable liquids at ambient temperatures to provide a flowable material of widely varying consistency; on the other hand, calcium sulfate is a powder to which a solubilizing liquid is added, which can increase preparation time. As discussed above, O'Leary expressly disclosed the compositions as being handle-able and moldable ("shape-sustaining but readily deformable"), as well as having improved consistency (the consistencies range, e.g., from "those which behave like putty to those which are runny"). O'Leary explicitly disclosed that a thickener can be added to make the composition easier and more convenient to apply. Therefore, since O'Leary addressed all of Yim's reasons for adding calcium sulfate, one skilled in the art would not be motivated to further add the calcium sulfate. In other words, there is no teaching, suggestion, or incentive to make the combination as suggested by the Examiner.

Applicants also submit that one skilled in the art reading Yim would not be motivated to combine demineralized bone to Yim's composition. Yim disclosed compositions wherein osteogenic proteins are utilized in the form of a pharmaceutically acceptable *solution* (including reconstitution from a lyophilized form). In particular, Yim disclosed that

It is optimal to solubilize the osteogenic protein at concentrations of at least about 1 mg/ml, preferably about 2 to 8 mg/ml, so that a pharmaceutically effective amount of protein can be delivered without undue volumes of carrier being necessary.¹⁰

Yim further disclosed that to prevent formation of particulates, a non-ionic surfactant can be added to the composition.¹¹

One skilled in the art reading Yim would not be motivated to add demineralized bone material (a source of osteogenic proteins) to Yim's compositions. Demineralized bone is not in

⁹ O'Leary col. 3, l. 49-52.

¹⁰ Yim col 3, l. 34-39 (emphasis added).

¹¹ *Id.* col. 4, l. 2-7.

the form of a pharmaceutically acceptable solution. Instead, demineralized bone is formed as *solid particles*, which Yim expressly wanted to eliminate. Thus, one skilled in the art reading Yim would not be motivated to combine demineralized bone matrix to Yim's composition.

With regard to claim 8 and its dependent claims, which recite a calcium sulfate, a mixing solution, a cellulose derivative, and a bioactive agent, these claims are patentable for at least the same reasons discussed above that claim 2 and its dependent claims are patentable. Similarly, claim 12, which recites a composition having a certain concentrations of components, is patentable for at least the same reasons discussed above. Applicants also note that neither O'Leary nor Yim disclosed or suggested a composition having the claimed concentrations of components.

Turning now to Jefferies, the Examiner relied on Jefferies for suggesting compositions having demineralized bone matrix along with calcium sulfate and a carrier, such as a cellulose derivative. As discussed in Applicants' previous response, Jefferies described multiple alternative compositions, but none of the compositions include demineralized bone, calcium sulfate, and a cellulose derivative. Indeed, Jefferies described 43 examples, but none of these examples includes calcium sulfate or a cellulose derivative, let alone the two in combination. Thus, while Jefferies was clearly aware of all the components in Applicants' claimed compositions, Jefferies did not disclose or suggest compositions having all the claimed components. Jefferies provides no motivation for Applicants' claimed compositions and therefore does not cure the deficiencies of the combination of O'Leary and Yim.

Finally, Applicants note that the Examiner dismissed the reasoning presented in the previously filed response because:

[a]pplicant's arguments are directed towards the references individually, and one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.¹²

Applicants again are not clear what this statement means. To the extent it means that Applicants did not explain why a person of ordinary skill in the art would not have been motivated to combine Yim's entire composition with O'Leary's entire composition, this has been

¹² Page 4 of the Office Action.

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addressed above. To the extent the statement means Applicants cannot overcome an obviousness rejection based on a combination of references by explaining why a person of ordinary skill in the art would not have been motivated to pick components from one reference and combine them with components in another reference, the statement is contrary to the law. As the Court of Appeals for the Federal Circuit explained in *Smithkline Diagnostics Inc. v. Helena Labs. Corp.*:¹³


A holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be "contrary to statute and would defeat the congressional purpose in enacting Title 35."

In light of the above remarks, Applicants submit that the claims are in condition for allowance, which action is requested.

Enclosed is a Petition for Extension of Time and the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: November 30, 2001



Tu N. Nguyen
Reg. No. 42,934

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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¹³ 8 USPQ2d 1468, 1475 (Fed. Cir. 1988).